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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14,23-26 and 44-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,23-26,44-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 9, 11, 12, 14, 23-26, and 44-53 are pending.

Applicant's traversal and the addition of claims 51-53 in paper filed on 2/27/06 are acknowledged and considered by the examiner.

Election/Restrictions

This application contains claims 11, 24, and 45 drawn to species (diabetic ischemic neuropathy or diabetic ischemic myocardial infarction) nonelected with traverse in Paper No. 7/7/02. A complete reply to the final rejection must include cancellation of nonelected species or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 11, 12, 14, 23, 24, 25, 26, and 48-49 remain and claims 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an PTO-1449), and Li et al. (US 6,066,123) in further view of Morishita et al. (EP 0847757). Isner teaches a method of treating limb ischemia in a subject using a nucleic acid encoding an endothelial cell mitogen selected from growth factor proteins, including hepatocyte growth factor (HGF). See pages 16-17. Isner teaches that the prior art has treated hindlimb ischemia in animal models using recombinant angiogenic growth factors (page 2). In addition, the prior art has "demonstrated that direct intramuscular injection of DNA encoding an angiogenic factor into ischemic tissue induces angiogenesis, providing ischemic tissue with increased blood vessels" (page 3). However, Isner does not specifically teach using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease in a subject. In addition, Isner does not specifically teach administering the nucleic acid once every few weeks or every few days to the subject.

However, at the time the invention was made, the problems with blood circulation deficiency in lower limb diabetic ischemic disease was well known to one of ordinary skill in the art. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98. In addition, there was a reasonable expectation of success for gene therapy using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98.

In addition, at the time the invention was made, short-term expression of a nucleic acid *in vivo* because of the short half-life of HGF and/or nucleic acid, and/or inactivation of the nucleic acid, and/or natural maturation and sloughing off of the transformed cell was well known to one of ordinary skill in the art and several applications (e.g., every few days or every few weeks) of the nucleic acid would be required to treat the ischemic disease in the subject. See Li et al. (column 8).

In addition, at the time the invention was made, Morishita teaches that the content of HGF gene in a medicament may be appropriately varied depending upon disease being treated, target organs, patient's age or body weight, etc. (page 5). It is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene. The dose may be divided into several days or a few months (page 5). Administering a nucleic acid encoding HGF using a Sendai virus (HVJ)-liposome was well known to one of ordinary skill in the art as exemplified by Morishita et al. (page 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the

relevant reports at the local news section of Japan Financial news paper dated 12/14/98, and Li et al. in further view of Morishita et al., namely to use a nucleic acid encoding HGF in a method of treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and use a nucleic acid encoding HGF in the method because of the problems with blood circulation is associated with lower limb diabetic ischemic disease and HGF is well known to one of ordinary skill in the art for treating problems with blood circulation.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98, and Li et al. in further view of Morishita et al., namely to administer a nucleic acid encoding HGF once every few days or every few weeks for treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer the nucleic acid encoding HGF once every few days or few weeks because of the problems associated with delivering nucleic acid in vivo.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner et al. taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998), Li et al. and Morishita et al., namely to use HVJ-liposome for delivering a nucleic acid encoding HGF in the method. One of ordinary skill in the art would have been motivated to combine the teachings, as a matter of designer's choice, and use HVJ-liposome for introducing the nucleic acid into the subject because HVJ-liposome is well known

to one of ordinary skill in the art for improving DNA delivery of a liposome comprising DNA to a cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 and Li et al., in further view of Morishita et al., namely to administer a nucleic acid encoding HGF, wherein at least 50 μg of the HGF is administered to the subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer at least 50 μg of the HGF because Morishita teaches that it is appropriate for one of ordinary skill in the art to administer HGF gene at a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when treating a disease.

> MPEP 2144.05 recites: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

This is the case here. The specification does not disclose that the limitation in instant claims is critical for one of ordinary skill in the art to practice the claimed invention.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 and Li et

al., in further view of Morishita et al., namely to administer a nucleic acid encoding HGF to the skeletal muscle of the ischemic site. One of ordinary skill in the art would have been motivated to combine the teachings to selectively administer the nucleic to ischemic site the and to provide ischemic tissue with increased blood vessels.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/27/06 have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., every few weeks) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With respect to claims 23-26, 44-47, 49-50, the argument is not found persuasive because the claimed method does not recite the limitation "every few weeks".

In response to applicant's argument that one of ordinary skill in the art would reasonably expect the HGF gene administration interval to be short, such as 1 to 2 days, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Other than applicant's assertion "one of ordinary skill in the art would reasonably expect the HGF gene administration to be short such as 1 to 2 days", there is no evidence of record to support applicant's assertion.

In response to applicant's argument that the effect of HGF gene was maintained even after 3 weeks and 5 weeks after its administration and such findings would not have been readily expected from the short half-life of HGF, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See In re Schulze. Other than applicant's assertion "such findings would not have been readily expected from the short half-life of HGF", there is no evidence of record to support applicant's assertion. In addition, one of ordinary skill in the art would reasonably expect the effect of HGF gene to be maintained after 3 to 5 weeks if is administered several times during the 5-week period.

In response to applicant's argument that administering the HGF gene less frequently lowers costs therefore providing an unexpected benefit, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See MPEP 716.01(c) (II), which recites that "The arguments of counsel cannot take the place of evidence in the record." Other than applicant's assertion "administering the HGF gene less frequently lowers costs therefore providing an unexpected benefit", there is no evidence of record to support applicant's assertion.

In addition, in response to applicant's argument that administering HGF gene less frequently would lower the cost, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). This is the case here. One of ordinary skilled in the art would understand that economics of using a product less frequently would result in a lower cost of using the product.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. Isner et al. taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998), and Li et al. (US 6,066,123) in further view of Morishita et al. teach the general conditions of treating lower limb diabetic ischemic disease. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In response to applicant's argument that determining the dosages would provide the desired therapeutic effect within such a wide dosages requires a significant amount of experimentation by one skilled in the art, the argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. See In re Schulze. Other than applicant's assertion "that determining the dosages would provide the desired therapeutic effect within such a wide dosages requires a significant amount of experimentation by one skilled in the art", there is no evidence of record to support applicant's assertion.

Applicant argues that without knowing that endogenous HGF in the diabetic lower limb ischemic disease model is much lower than that of control, one skilled in the art would not have been motivated to determine an appropriate dose of HGF gene for treating diabetic ischemic disease.

Applicant's argument is not found persuasive because one of ordinary skill in the art (Professor Ogihara) teaches the HGF has been found to have vascular regeneration activity. See Gene Therapy of Osaka University, English translation from the Japan Financial News Paper,

Local News Section (Dec. 14, 1998). In addition, the prior art teaches that the complications of diabetes are the result of blood circulation deficiency by arterial occlusion in the limb. Thus, one of ordinary skill in the art would have been motivated to use HGF gene therapy to treat lower limb diabetic ischemic disease. Thus, the general conditions for treating diabetic ischemic disease using HGF gene therapy were known to one of ordinary skill in the art. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 44-47 and 50 remain and claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isner et al. (WO 98/19712, cited on a PTO-1449) taken with Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an PTO-1449) in further view of Morishita et al. (EP 0847757).

Isner teaches a method of treating limb ischemia in a subject using a nucleic acid encoding an endothelial cell mitogen selected from growth factor proteins, including hepatocyte growth factor (HGF). See pages 16-17. Isner teaches that the prior art has treated hindlimb ischemia in animal models using recombinant angiogenic growth factors (page 2). In addition, the prior art has "demonstrated that direct intramuscular injection of DNA encoding an angiogenic factor into ischemic tissue induces angiogenesis, providing ischemic tissue with increased blood vessels" (page 3). However, Isner does not specifically teach using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease in a subject.

However, at the time the invention was made, the problems with blood circulation deficiency in lower limb diabetic ischemic disease was well known to one of ordinary skill in the art. See English translation of the relevant reports at the local news section of Japan Financial

news paper dated 12/14/98. In addition, there was a reasonable expectation of success for gene therapy using a nucleic acid encoding HGF to treat diabetic lower limb ischemic disease. See English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98.

In addition, at the time the invention was made, Morishita teaches that the content of HGF gene in a medicament may be appropriately varied depending upon disease being treated, target organs, patient's age or body weight, etc. (page 5). It is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene. The dose may be divided into several days or a few months (page 5). Administering a nucleic acid encoding HGF using a Sendai virus (HVJ)-liposome was well known to one of ordinary skill in the art as exemplified by Morishita et al. (page 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Morishita et al., namely to use a nucleic acid encoding HGF in a method of treating lower limb ischemic disease in a subject. One of ordinary skill in the art would have been motivated to combine the teachings and use a nucleic acid encoding HGF in the method because of the problems with blood circulation is associated with lower limb diabetic ischemic disease and HGF is well known to one of ordinary skill in the art for treating problems with blood circulation.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner et al. taken with Gene

Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998), and Morishita et al., namely to use HVJ-liposome for delivering a nucleic acid encoding HGF in the method. One of ordinary skill in the art would have been motivated to combine the teachings, as a matter of designer's choice, and use HVJ-liposome for introducing the nucleic acid into the subject because HVJ-liposome is well known to one of ordinary skill in the art for improving DNA delivery of a liposome comprising DNA to a cell.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Morishita et al., namely to administer a nucleic acid encoding HGF, wherein at least 50 μg of the HGF is administered to the subject. One of ordinary skill in the art would have been motivated to combine the teachings and administer at least 50 μg of the HGF because Morishita teaches that it is appropriate to administer a dose of 0.0001 mg to 100mg, preferably 0.001 mg to 10 mg when calculated as the HGF gene.

> MPEP 2144.05 recites: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

This is the case here. The specification does not disclose that the limitation in instant claims is critical for one of ordinary skill in the art to practice the claimed invention.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Isner taken with English translation of the relevant reports at the local news section of Japan Financial news paper dated 12/14/98 in further view of Morishita et al., namely to administer a nucleic acid encoding HGF to the skeletal muscle of the ischemic site. One of ordinary skill in the art would have been motivated to combine the teachings to selectively administer the nucleic acid to the site and to provide ischemic tissue with increased blood vessels.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/27/06 have been fully considered but they are not persuasive for the reasons set forth above. The argument was already addressed above under the prior rejecton.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

BRIAN WHITEMAN
PATENT EXAMINER